Decision Memo for Positron Emission Tomography (FDG) for Alzheimer's Disease/Dementia (CAG-00088N)

Decision Summary

As described in this decision memorandum, we have analyzed the medical and scientific evidence submitted with the request for a national coverage decision, as well as additional information obtained as a result of our own investigation. The TA demonstrates that adding an FDG-PET scan to the standard work-up of AD does not improve upon the practice of routinely treating patients with the diagnosis of mild cognitive impairment or dementia of possible or probable AD type, as defined by AAN clinical guidelines. Our analysis concludes that the addition of an FDG-PET scan to the standard evaluation of AD does not result in improved patient outcomes.

Therefore, we have determined that the available evidence is adequate to conclude that an FDG-PET scan is not reasonable and necessary when used in the diagnosis and management of early dementia in elderly patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease.

Therefore, we intend to continue our national noncoverage decision. This noncoverage policy will apply to those patients that present with cognitive decline (i.e., suspected dementia) and are clinically diagnosed with age-related memory impairment, MCI, or mild, moderate or severe dementia. Patients along this clinical continuum of cognitive decline encompass those for whom AD is suspected as a contributing etiology and specifically includes patients diagnosed with possible or probable AD by AAN-recommended criteria and those diagnosed with other neurodegenerative diseases with or without AD.

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Decision Memo

This decision memorandum does not constitute a national coverage determination (NCD). It states CMS's intent to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction giving specific directions to our claims-processing contractors. That manual issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.

TO: Administrative File: CAG #00088A
FDG-Positron Emission Tomography (FDG-PET) for Alzheimer's disease/Dementia

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SUBJECT: Coverage Decision Memorandum for FDG- Positron Emission Tomography for diagnosis of early dementia in certain geriatric patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease.

DATE: April 16, 2003

This memorandum serves four purposes: (1) provides clinical background on Alzheimer's Disease (AD) and FDG-PET; (2) reviews the history of Medicare coverage of FDG-PET and provides a timeline of CMS activities related to the coverage process; (3) presents and analyzes the relevant scientific and clinical data related to the use of FDG-PET scans in the diagnosis of early dementia in certain geriatric patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease; and (4) outlines the agency's intention to maintain its noncoverage determination under the statutory authority of section 1862 (a)(1)(A) of the Social Security Act (the Act).

Clinical Background

Alzheimer's disease (AD) is an age-related and irreversible brain disorder that occurs gradually and results in memory loss, behavior and personality changes, and a decline in thinking abilities. AD is the most common cause of dementia, representing approximately two -thirds of cases. More rare neurodegenerative conditions include frontotemporal dementia and dementia with Lewy bodies. The term dementia does not imply a specific cause or pathologic process and is usually defined as a syndrome presenting with memory impairment in an alert patient plus one or more of a variety of cognitive symptoms. These include aphasia (problem understanding or expressing language), apraxia (problem performing complex purposeful movements), agnosia (problem identifying objects), and difficulties with executive functioning (making everyday decisions).

The course of AD varies among individuals, as does the rate of decline. On average, patients with this disease live 8-10 years after they are diagnosed, although the disease can last for up to 20 years. It is estimated that about 4,000,000 people in the United States have AD.[1] Alzheimer's disease is typically not reported on death certificates; therefore, estimates of prevalence (how many people have a disease at any one time) are based upon community surveys. The prevalence of AD climbs steadily after age 65 so that 30% to 50% of persons in the 8th or 9th decade have AD.

Most people with AD present with symptoms of cognitive decline after age 60. The earliest symptoms characteristically include loss of recent memory, later compounded by faulty judgment and changes in personality. Often, people in the initial stages of AD think less clearly and tend to be easily confused. Later in the disease, they may forget how to do simple tasks, such as how to dress themselves or eat with proper utensils. Eventually, people with AD lose the capacity to function on their own and become completely dependent upon other people for their everyday care. Finally, the disease becomes so debilitating that patients are bedridden and are likely to develop other medical conditions. Most commonly, people with AD die from pneumonia.

Although the risk of developing AD increases with age, AD and dementia symptoms are not a part of normal aging. In the absence of disease, the human brain often can function well into the tenth decade of life. Use of research criteria in clinical studies of aging and cognitive impairment has yielded three groups of subjects: normal elderly, those who are demented, and a third group of individuals who cannot be classified as normal or demented but who are cognitively (usually memory) impaired. Mild cognitive impairment (MCI) refers to the intermediate clinical state of cognition and functional ability between normal aging and mild dementia.[2]

The most accurate diagnosis of AD is based upon specific findings in brain tissue at autopsy. Typical microscopic findings are neuritic plaques between neurons and neurofibrillary tangles inside neurons.[3] Glucose metabolism in affected areas decreases as the disease progresses, providing the basis, as discussed later, for the use of FDG-PET. The degree of clinical cognitive impairment, however, may not directly correlate with the severity of Alzheimer-type pathology. The pathological changes of AD frequently coexist with other lesions affecting cognition such as vascular infarcts ("mixed dementia"). There is increasing evidence of the additive effects of vascular pathology and AD-type changes in the development of cognitive decline.[4]

The diagnosis of possible or probable AD during the life of a person is made when the patient has dementia typical of AD in its clinical course and does not have a condition that may mimic AD in the early stages of disease (such as cerebrovascular disease, depression, or a metabolic disorder). There are no established biological markers for the diagnosis of AD. The standard clinical evaluation currently recommended by the American Academy of Neurology (AAN) includes a complete history and physical, neuropsychiatric evaluation, laboratory testing and anatomical neuroimaging to rule out other diseases.[5] If a patient with cognitive impairment does not meet the diagnostic criteria for dementia, then a diagnosis of MCI may be used. For most patients with MCI and for some patients in the early stages of dementia, diagnosis often depends on the observation of clinical progression over repeated patient visits.

Functional neuroimaging, such as FDG-PET, has been proposed for the evaluation of elderly patients who may have early dementia and for whom the differential diagnosis includes one or more kinds of neurodegenerative disease. Positron emission tomography (PET) is a diagnostic imaging procedure that assesses the level of metabolic activity and perfusion in various organ systems of the human body. Images are obtained from positron emitting radioactive tracer substances (radiopharmaceuticals) that are usually administered intravenously to the patient. 2-[F-18] Fluoro-D-Glucose (FDG) is a radioactive tracer substance that emits sub-atomic particles, known as positrons, as it decays. A positron camera (tomograph) is used to measure the decay of radioisotopes such as FDG. The rate of FDG decay provides biochemical information on the rate of glucose metabolism in the tissue. For instance, as malignancies can cause abnormalities of metabolism and blood flow, FDG-PET evaluation can indicate the probable presence or absence of malignancy based upon observed differences of biologic activity.

FDG-PET may be able to diagnose AD by identifying anatomical patterns of brain hypometabolism, which typically occur bilaterally in the temporal and parietal lobes. FDG-PET scans typical of AD may be differentiated by visual inspection from scans suggestive of vascular dementia (asymmetric and focal abnormalities) and scans indicative of frontal lobe or lobar dementias (marked hypometabolism of frontal or temporal lobes with sparing of parietal lobes).

There is not a known treatment to prevent or cure AD. Current drug therapies are aimed at symptomatic relief and at slowing disease progression. Use of cholinesterase inhibitors (AChE-I) is thought to correct the central cholinergic deficit in persons with AD and has shown beneficial effects relative to placebo in randomized clinical trials, modestly delaying progression of disease in some individuals with mild to moderate dementia.[6] Subjects in these clinical trials have generally been patients with a history of gradual cognitive decline and a diagnosis of probable AD based upon criteria recommended by the AAN.[7] No trials have been done using FDG-PET-based diagnosis of Alzheimer's disease as an entry criterion.

AChE-I therapy may also reduce the rate of institutionalization in patients with more severe dementia.[8] However, whether the reported improvement in cognition translates into clinically important effects on a patient's functional ability remains an issue of debate.[9] Significant adverse events are uncommon with currently recommended and FDA-approved agents, which include donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl). Drug therapy has been studied in populations with prior medical and co-morbid conditions, including patients taking one or more concomitant medications, and was shown to be well-tolerated, producing no clinically significant drug-drug interactions or changes in metabolic, cardiovascular, hepatic, or renal function. Few patients withdraw due to adverse events. For example, in a multi-national double-blind placebo-controlled trial, roughly 15% withdrew from the AChE-I group compared with 10% from the placebo group. The most frequently experienced side effects are associated with the digestive system (nausea, vomiting, diarrhea) and most are mild and transient in nature, usually resolving during continued drug use.[10]

History of Medicare Coverage for FDG-PET

CMS previously reviewed scientific literature and established coverage for many uses of FDG -PET. FDG-PET is currently covered for uses in the evaluation of solitary pulmonary nodules, lung cancer (non-small cell), esophageal cancer, colorectal cancer, lymphoma, melanoma, refractory seizures, myocardial viability, and breast cancer. For each indication, there are specific coverage limitations listed in the CMS Coverage Issues Manual, Section 50-36, [11] and the related coverage decision memorandum published on December 15, 2000.[12] A tracking sheet was posted on May 15, 2001 stating that uses of FDG-PET for Alzheimer's and other dementias would be reviewed for possible expansion of the previous coverage decision and be referred to Medicare Coverage Advisory Committee (MCAC) for assistance.

Timeline of Recent Activities

Date	Activity
December 15, 2000	The Decision Memorandum for the initial broad coverage request for FDG-PET was posted on the coverage website. CMS referred the request for use of FDG-PET in AD to MCAC for review.
April 2001	CMS met with the Agency for Health Research and Quality (AHRQ) to discuss development of a Technology Assessment (TA) on FDG-PET for AD.
May 2001	CMS formally commissioned a TA from AHRQ on the use of FDG-PET and other neuroimaging techniques in the diagnosis and management of AD/dementia.
June 14, 2001	The MCAC Executive Committee (EC) met to assist CMS and AHRQ with problem formulation and the development of analytic questions for the TA.

August 2001	AHRQ selected the Center for Clinical Health Policy Research at Duke University as the evidence-based practice center (EPC) for the TA.
October 2001	The University of California at Los Angeles (UCLA) amended the original request for coverage to state: FDG-PET when used to assist with the diagnosis of early dementia in certain geriatric patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease.
January 10, 2002	The Diagnostic Imaging (DI) panel of the MCAC convened to review the evidence, to hear public testimony and to issue recommendations to CMS on the use of FDG-PET for AD.
April 16, 2002	The MCAC EC met to review the DI panel recommendations.

Food and Drug Administration (FDA) Status

The FDA approved the following uses for FDG F 18 in a Federal Register notice dated March 10, 2000:

“The [FDA] Commissioner has concluded that FDG F 18 injection, when produced under the conditions specified in an approved application, can be found to be safe and effective in FDG -PET imaging in patients with [coronary artery disease] CAD and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function, as discussed in section III.A.1 and III.A.2 of this document. The Commissioner also has concluded that FDG F 18 injection, when produced under the conditions specified in an approved application, can be found to be safe and effective in FDG-PET imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer, as discussed in section III.A.1 and III.A.3 of this document. In addition, manufacturers of FDG F 18 injection and sodium fluoride F 18 injection may rely on prior agency determinations of the safety and effectiveness of these drugs for certain epilepsy-related and bone imaging indications, respectively, in submitting either 505(b)(2) applications or [amended new drug applications] ANDA's for these drugs and indications.” [13]

The FDA approval language cited above indicates that FDG F 18 is not currently approved by the FDA to assist in the diagnosis of early dementia in patients with possible neurodegenerative disease. Therefore this use of FDG-PET imaging would represent an off-label use.

Benefit Category

In the preamble to a final rule published on November 1, 2002, CMS noted:

Section 1861(t)(1) provides that the terms drugs and biologicals ‘‘include only such drugs (including contrast agents) and biologicals, respectively, as are included (or approved for inclusion) in [one of several pharmacopoeias] (except for any drugs and biologicals unfavorably evaluated therein), or as are approved by the pharmacy and drug therapeutics committee (or equivalent committee) of the medical staff of the hospital furnishing such drugs and biologicals for use in such hospital.’’ A careful reading of this statutory language convinces us that inclusion of an item in, for example, the USPDI … does not necessarily mean that the item is a drug or biological. Inclusion in such reference (or approval by a hospital committee) is a necessary condition for us to call a product a drug or biological, but it is not enough. Rather, if we are to call a product a drug or a biological for our purposes, CMS must still make its own determination that the product is a drug or biological…[14]

Therefore the appropriate benefit category for all diagnostic radiopharmaceuticals is 1861(s)(3) which includes diagnostic X-ray tests, diagnostic laboratory tests, and other diagnostic tests. We will consider neither diagnostic nor therapeutic radiopharmaceuticals to be drugs as described in section 1861(t).[15]

Summary of Evidence

In addition to commissioning a TA to assist in the review process and participating in MCAC deliberations, CMS requested information from experts and professional societies, reviewed evidence-based practice guidelines, position papers, and additional submitted and related scientific literature.

Technology Assessment

CMS commissioned a TA from AHRQ to review the existing scientific evidence with regard to the role of FDG-PET in assisting with the diagnosis of early dementia in elderly patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease. CMS consulted the MCAC EC for assistance in developing the evaluation questions and TA design.

AHRQ presented the proposed analytic framework to the MCAC EC, which provided comments on the proposed questions, the objective of the TA, and the decision model. The objective of the TA was to assess the likely health outcomes of FDG-PET scanning in patients with dementia, in patients with mild cognitive impairment (MCI), and in asymptomatic patients with a family history of AD, all subsequent to the standard clinical evaluation as described in the American Academy of Neurology (AAN) guidelines.[16] These health outcomes would then be compared to those derived from a strategy based on the standard clinical evaluation without further testing. Specific questions corresponding to the three scenarios were:

Scenario A: In patients with dementia, could PET be used to determine the type of dementia, thus facilitating early treatment of AD?

Scenario B: For patients with MCI, could PET be used to identify a group of patients with a high probability of AD so that they could start early treatment?

Scenario C: Is the available evidence adequate to justify the use of PET in asymptomatic patients with a family history of AD (i.e., first-degree relatives) so that they could start early treatment?[17]

AHRQ selected the Duke University Evidence-based Practice Center (EPC) to produce the TA. The TA was submitted to the DI panel and the MCAC EC for use in preparing their recommendations to CMS.[18]

Decision Modeling

The strongest support of clinical benefit for a diagnostic test would be derived from direct evidence from a randomized control trial. Such a trial would randomize patients to receive a conventional evaluation or an evaluation that includes the new test, an FDG-PET scan in this case. The primary study measure would be a clinical outcome that corresponds to the health burden of the disease. Study outcomes of interest could include treatment decisions, health outcomes, caregiver arrangements and other outcomes deemed to be important in patients with dementia. No study of FDG-PET in patients who may have AD has provided this level of evidence. Thus, in the absence of direct evidence, the TA relied upon indirect evidence to evaluate use of FDG-PET in patients who present with suspected AD.

While indirect evidence is less persuasive than direct evidence, it can be used to establish links in a logical chain. In this case the links occur between 1) FDG-PET use and diagnosis of AD, 2) diagnosis of AD and treatment decisions, and 3) treatment decisions and clinical outcomes. The EPC reviewed the scientific evidence regarding the performance of FDG-PET, the natural history of AD, and the efficacy and adverse effects of drug therapy for AD, and created a decision model linking testing with treatment and outcome. Thus, through the use of a Markov model, the TA linked the available evidence to determine if use of FDG-PET would lead to more accurate diagnosis of AD and if a more accurate diagnosis of AD could (via appropriate treatment) lead to a clinically meaningful benefit.

TA Methods

Search strategy and selection criteria. The authors of the report searched the MEDLINE, CINAHL and HealthStar databases from January 1996 to January 2001 for studies describing the operating characteristics (i.e., sensitivity and specificity) of FDG-PET. They identified 18 articles published in peer-reviewed journals, each containing original data on more than twelve human subjects relevant to the efficacy of FDG-PET in the diagnosis of AD. The reference standard used was either histopathology or clinical diagnosis. To identify parameter estimates related to natural history of AD and drug treatment of AD that were needed for the decision model, the EPC focused on identifying existing systematic reviews, meta-analyses, or independent studies. In addition to referring to literature on previous decision models, the authors sought recommendations for high-quality studies from their local and consultant experts, resulting in ninety-four articles used for estimates of inputs other than FDG-PET operating characteristics.

Data collection. The EPC used information from the selected studies to construct evidence tables and a summary receiving operating characteristic (S-ROC) curve for the test in diagnosing AD. FDG-PET test performance, natural history, and quality of life studies were used to provide baseline and range estimates for an integrative model. This integrative model was a Markov decision model constructed using DATA 3.5 software.[19]

Integrative model. The model was constructed to address the following question: For a patient with a given state of cognitive function, which strategy is more likely to provide better health outcomes? As described above, the specific cognitive states considered were 1) mild or moderate dementia, 2) mild cognitive impairment (MCI), and 3) asymptomatic with a first-degree relative having AD.[20] All patients were assumed to have completed a standard clinical evaluation such as recommended by the AAN. The model therefore evaluated whether FDG-PET provided additional clinical value beyond a standard clinical evaluation as defined by the AAN.

The strategies examined were 1) no further diagnostic testing and no treatment (i.e., conceptually equivalent to the placebo arm in a clinical trial), 2) further testing with FDG-PET and treatment of patients with positive FDG-PET results and 3) no further testing but treatment of all patients meeting standard clinical evaluation diagnostic criteria for AD as defined by AAN guidelines. The decision model produced estimates of life expectancy, quality-adjusted life expectancy, and life expectancy free of severe dementia. The model provided quantitative projections of these relevant clinical outcomes to address the following questions for each of the three clinical scenarios of interest:

1. What are the possible clinical management options and corresponding expected outcomes for the scenario?
2. What is the diagnostic performance of FDG-PET in the scenario?
3. What are the benefits and adverse effects of treatment options that might be used in the scenario?
4. For a patient with a given state of cognitive function, which strategy is most likely to provide better health outcomes?

Variable projections. In addition to a base case analysis geared to the "typical" individual in each scenario, the EPC performed extensive sensitivity analyses to evaluate the robustness of the projections. Given the possibility that more effective treatments might become available that may also have greater side effects than the current treatments, or that test accuracy may increase in the future, the sensitivity analyses allowed for an evaluation of hypothetical scenarios not supported by the current evidence.

The structural and estimation assumptions built into the model were constructed to be unbiased for or against testing. The authors chose assumptions that would favor testing when this was not possible. A number of clinical and methodological expert consultants and peer reviewers validated the assumptions as well as the description of Markov model states.[21] The TA report was peer-reviewed and, once approved by AHRQ, became an official document of that agency.

TA Results

Test operating characteristics. The pooled sensitivity estimate for FDG-PET resulting from the TA systematic review of the literature and meta-analysis was 88% (95% confidence interval = 79% - 94%), and the pooled specificity estimate was 87% (77% - 93%) for distinguishing normal healthy controls from patients with AD. The rate of underlying AD in patient groups with dementia and MCI receiving additional FDG-PET testing was drawn from the estimated prevalence rate for AD in these populations. In the base case analysis for patients with mild-to- moderate dementia, the rate of underlying AD following a standard clinical evaluation was set at 56%. Although the standard clinical evaluation has been shown to be more accurate than this prevalence rate in identifying AD, this low estimate for the model takes into account the notion that a substantial proportion of patients with symptoms of dementia present in primary care settings, where a clinical evaluation may be less rigorous than that performed in a specialty center. The conclusion of the analysis is less favorable to FDG-PET if this estimate increases (as would be expected with a complete clinical evaluation conducted in a specialty clinic). Prevalence of AD in patients clinically diagnosed with MCI was estimated at 80%.

Scenario A. For the base case analysis in patients with mild to moderate dementia as determined by the AAN criteria, treating all patients with possible or probable AD after a standard clinical evaluation was the preferred strategy. This strategy was superior to treating based upon an additional test using FDG-PET in quality-adjusted life years (QALYs), life expectancy (LE) or severe-dementia-free life expectancy (SDFLE). The absolute differences were 0.01 QALY, 0.01 years of LE, and 0.02 years of SDFLE, respectively, in favor of treatment without further testing. The difference between the strategies was small, but proved robust in sensitivity analyses. The key reason that treatment following clinical evaluation without further testing is superior, is that the increase in the false negative rate resulting from FDG-PET testing may lead to withholding potentially effective and relatively benign treatment from those patients.

Scenario B. For patients with MCI, the results of the analysis were virtually the same as for patients with mild-to-moderate dementia under the assumption that treatment efficacy was the same as that for dementia patients.

Scenario C. For asymptomatic individuals with an elevated risk, a strategy to treat all patients was preferred in the base case under the assumption that treatment was effective in this population.

TA Conclusions

Based upon a systematic literature review, meta-analysis and decision analysis, the TA authors had the following four major conclusions regarding the use of FDG-PET in patients who may have AD.

- "For patients with dementia who have had a recommended clinical evaluation, treatment without further testing is superior to treating based on an additional test using FDG-PET. Since treatment for this clinical scenario has been shown to be moderately effective and relatively benign, the increase in true negatives (i.e., those who did not need the treatment) resulting from use of FDG-PET is overshadowed by the concomitant increase in false negatives (i.e., those who would benefit from treatment but for whom it would be withheld if they were not identified as positives).
- If the evidence for treatment efficacy of AChE-I agents in patients with dementia can be extrapolated to patients with MCI, then empiric treatment of these patients would also be superior to treating based upon FDG-PET. This is because the proportion of MCI patients with AD is comparable to – and may be higher than – the proportion of demented patients with AD. Even if survival is not improved, earlier treatment should improve the proportion of time a patient is alive with a lesser degree of impairment.
- If the evidence for treatment efficacy of AChE-I agents in patients with dementia can be extrapolated to patients who are asymptomatic but have an elevated risk for AD, then empiric treatment of these patients would be superior to treating based on FDG-PET.
- FDG-PET scanning could be of value if a new treatment were to be developed that was more effective but had a higher risk of one or more of a variety of highly negative consequences such as a reduction in quality of life, inducing progression of disease, or death." [22]

Additional Studies Reviewed

CMS reviewed and made available to the MCAC an unpublished manuscript authored by Daniel Silverman, MD, PhD, and by other requestors and colleagues from UCLA, with the running title of "Clinical Benefit of Incorporating FDG-PET into the Evaluation of Early Dementia." The document described a decision model comparing outcomes from two approaches to the evaluation of patients with early symptoms of cognitive decline. The first strategy utilized the standard clinical evaluation recommended by the AAN and the second approach incorporated FDG-PET to test for the presence of a pattern of regional metabolism characteristic of AD. The authors concluded that use of FDG-PET for evaluating early dementia in the elderly would increase diagnostic accuracy by decreasing rates of false negative and false positive diagnoses of AD compared to the AAN-recommended strategy. Use of this strategy would reduce the need for nursing home care and unnecessary drug therapy.[23]

MCAC Summary

The MCAC EC met in June 2001, to assist CMS and AHRQ with problem formulation and the development of analytic questions for the TA.[24] The TA was completed on December 14,2001 . On January 10, 2002, the MCAC DI panel deliberated on the use of FDG-PET in the diagnosis and management of AD and other dementias in the elderly and made its recommendation regarding the evidence of efficacy to the MCAC EC. The panel unanimously voted “No” to the following questions:

1. Is the evidence adequate to demonstrate that FDG-PET has clinical benefit in evaluating patients with possible or probable AD as defined by the current AAN guidelines?
2. Is the evidence adequate to demonstrate that FDG-PET has clinical benefit in evaluating patients with MCI as defined by the current AAN guidelines?

At the subsequent MCAC EC meeting on April 16, 2002, there was a discussion of the precise definitions of the terms “suspected dementia”, “early dementia”, “mild cognitive impairment”, “suspected AD”, “early AD”, and “possible and probable AD” that are key in specifying the various subgroups presenting with cognitive decline. Clinicians from UCLA proposed a categorization of patients that may have AD-specific anatomic lesions and who would be candidates, in their view, for testing with FDG-PET. Categories included 1) dementia syndrome, 2) dementia of possible or probable AD cause, 3) non-AD dementia, 4) MCI, and 5) “age-associated memory impairment.” UCLA participants were concerned that patient groups may have been excluded from consideration when the panel substituted the terms “possible or probable AD” for “suspected AD” in one of the voting questions. However, after deliberating and reviewing the recommendations of the DI panel, the MCAC EC accepted the DI panel’s change and determined that the terms utilized in the two questions voted on by the DI panel covered all relevant categories. The EC proceeded to unanimously ratify the DI panel’s recommendations.[25]

Position Statements

The Quality Standards Subcommittee of the AAN, charged with developing practice parameters, recently published three systematic reviews addressing major issues in the diagnosis and management of dementia in the elderly.[26] [27] [28] These evidence-based reports seek to reflect scientifically sound, clinically relevant guidelines for physicians and are formally endorsed as policy by the AAN. The most recent Report of the Quality Standards Subcommittee of the AAN on the diagnosis of dementia published in 2001 states:

“PET scanning appears to have promise for use as an adjunct to clinical diagnosis, but further prospective studies with PET are needed to establish the value that it brings to diagnosis over and above a competent clinical diagnosis (…) PET imaging is not recommended for routine use in the diagnostic evaluation of dementia at this time”.[29]

In response to the posting of this issue on the CMS website, MCAC meetings and at the request of CMS, position statements regarding the use of FDG-PET for the diagnosis of AD and other dementias were received from the American College of Radiology (ACR), the National Electric Manufacturers Association (NEMA), the Alzheimer's Association, and the Society of Nuclear Medicine. Unlike the AAN evidence-based guidelines, these statements are letters representing the views of the organizations involved rather than a formal scientific review.

- ACR "…does not support the coverage of PET for Alzheimer's at this time because its usefulness in the clinical management of diseases without viable treatment is unsubstantiated…."[30]
- NEMA "…is in support of Medicare coverage of PET for use in the diagnosis of AD..." They believe that "[the] use of PET will allow the clinician to slow the progress of AD and allow increased quality of life years for the patients as well as ease the onerous burdens imposed on caregivers."[31]
- The Alzheimer's Association "...[does] not agree that PET scans should be a routine part of the diagnostic process." This association believes that "...at this time, the potential of PET remains an experimental goal.... repeated studies have shown that properly trained evaluators can identify Alzheimer's disease correctly 90 to 95% of the time." [32]
- The Society of Nuclear Medicine "…offered strong support for the addition of Alzheimer's disease as a CMS reimbursable indication for FDG-PET scanning." This organization believes that "…FDG-PET is more effective than the clinical examination for the differential diagnosis and identification of various dementia causes; PET enables physicians to clearly identify and differentiate between various types of dementia; the usefulness of PET is important for patient quality of life." [33]

Expert Opinion

CMS also received written statements, including two letters, from individual experts with an interest in the coverage decision. Documents included were:

- An opinion statement from a representative of the Alzheimer's Research Foundation stating: "…Physicians must use any and all tests available to rule out any of the dozen – plus conditions/pathologies that can mimic Alzheimer's. FDG-PET has proven consistently above 90% sensitivity for AD, but its specificity is among the lowest of available modes of testing, often as low as 50%. This tends to lessen its value somewhat in the confirmation process."[34]

- A letter from the Chair of the AAN behavioral neurology section, the Co-chair of the AAN practice parameters committee on dementia, and another member of such committee. Two of the signatories were also initiators of the request for coverage. They recommended that FDG-PET be “approved for coverage in the diagnosis and differential diagnosis of AD and other dementing disorders”. [35] The letter reflected the authors’ views as individuals and did not represent AAN policy.

In addition to clinical effectiveness relative to a standard clinical evaluation, the expert opinion reflected in these documents (as well as the decision model draft manuscript described above) raised a number of clinical issues relevant to the use of FDG-PET in the diagnosis and management of early dementia and AD. These included 1) the effects of FDG-PET use on provider prescribing behavior and patient adherence to drug treatment; 2) psychosocial labeling effects of FDG-PET on patients with early dementia; 3) potential of FDG-PET to improve detection of AD in primary care settings; 4) projected effects of FDG-PET use on resource utilization (e.g., medical visits, use of anatomical imaging, nursing home placement), and 5) efficacy and adverse effects of available drug therapies. These and other relevant clinical topics are addressed in the CMS Analysis section below.

Public Comments

CMS received no additional public comments.

CMS Analysis

National coverage determinations (NCDs) are determinations made by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act, § 1869(f)(1)(B). In order to be covered by the Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not otherwise be excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member”, § 1862(a)(1)(A).

CMS has issued regulations pertaining to the coverage of diagnostic tests under the Medicare part B program. Those rules provide that, except for a few exceptions, diagnostic tests must be ordered by the physician who treats the beneficiary for a specific medical problem, and the physician must use the results in the management of the beneficiary's specific medical problem (42 C.F.R. § 410.32). In general, tests not ordered by the treating physician who is treating the beneficiary are not reasonable and necessary. See also 42 C.F.R. § 411.15(k)(1).

The outcome to assess in any diagnostic test involves the downstream consequences of the diagnostic test and the comparison of these to the consequences and outcomes of an alternative diagnostic test or strategy. In this case, FDG-PET testing has been proposed as an addition to the various diagnostic procedures and tests that comprise the standard clinical evaluation for AD. The standard clinical evaluation currently recommended by the American Academy of Neurology includes a complete history, physical and neuropsychiatric evaluation, laboratory testing and structural neuroimaging. The decision to test with FDG-PET in addition to the standard clinical evaluation should be made only when the results of FDG-PET will influence treatment decisions and thereby have the potential to improve health outcomes.

The strongest support of clinical benefit for a diagnostic test is derived from direct evidence from a randomized control trial. Such a trial would randomize patients to receive the standard clinical evaluation or an evaluation that includes the new test, an FDG-PET scan in this case. The primary study measure would be a clinical outcome that corresponds to the health burden of the disease. Study outcomes could include treatment decisions, health outcomes, caregiver arrangements, and other outcomes deemed to be important in patients with symptoms of dementia. No study of FDG-PET in patients who have mild cognitive impairment or dementia has provided this level of evidence. In the absence of direct evidence, indirect evidence was used to construct a model to quantitatively evaluate the use of FDG-PET in elderly patients who present with symptoms of dementia. [36]

The decision model assessed the health outcomes of FDG-PET scanning in patients with mild to moderate dementia, and with mild cognitive impairment (MCI) following a standard clinical evaluation consistent with AAN guidelines. The health outcomes for both target populations resulting from this strategy were then compared to those derived from a strategy based upon the standard clinical evaluation without further neuroimaging testing.

The standard clinical evaluation of cognitive impairment recommended by the AAN is the most appropriate diagnostic reference standard for comparison with the proposed additional test. This type of clinical evaluation is the most widely studied approach in the research literature. More importantly, a number of randomized clinical trials have established its ability to select patients who will benefit from pharmacologic treatment. Evidence of treatment benefit for probable AD has been shown only for patients with cognitive impairment selected and stratified based on the standard clinical evaluation. Patients identified with mild-to-moderate dementia of probable AD type by standard clinical evaluation who received AChE-I have shown slower disease progression than controls.[37]

The TA results indicate that use of FDG-PET would not be the preferred management strategy. Individuals who present with dementia or MCI, for which the standard clinical evaluation has shown no cause for their cognitive failure other than possible or probable AD, are candidates for treatment with AChE-I medications as well as other supportive interventions. Were FDG-PET to be added to an initial standard clinical evaluation, a non-trivial proportion of patients who would be candidates for treatment with AChE-I would be found to be negative on FDG-PET. In the decision model base case analyses, the false negative rate with FDG-PET [38] would increase from 0 to 7% for patients with mild dementia, and from 0 to 10% in patients with MCI.[39] It is possible that knowledge of a negative FDG-PET test result would influence patients or physicians to forego drug treatment when they might otherwise benefit. The use of FDG-PET would also effectively increase the true negative rate resulting from the clinical evaluation and would thus help avoid treatment of individuals who do not have underlying AD. As discussed below, though, these patients may in fact benefit from treatment. For the base case analyses, the true negative rate[40] would increase from 0 to 38% for patients with mild dementia, and from 0 to 17% in patients with MCI. [41]

The trade-off between the increase in false negatives and the increase in true negatives resulting from the use of FDG-PET is central to the interpretation of the evidence by CMS. The expected scenario of more false positive cases being treated after a standard clinical evaluation alone is preferable to the scenario of failing to treat the false negatives resulting from adding FDG-PET to the standard clinical evaluation. This preference is justified by the absence of serious complications and relatively high tolerance for AChE-I therapy.

This preference is further justified by the fact that the decision model in the TA incorporated a structural assumption that would favor testing, namely that “treatment benefits only those individuals with underlying AD.”[42] However, it cannot be assumed that increased accuracy in selecting persons with AD-specific lesions is equivalent to increased ability in selecting persons who will benefit from drug therapy. Even if use of FDG-PET results in more accurate identification of patients with the anatomical lesions characteristic of AD, it has not been shown that drug treatment benefit accrues specifically to patients with anatomic findings characteristic of AD.[43] No treatment studies have yet been done on patient populations identified by FDG-PET. In the absence of direct evidence, it is not possible to conclude that only patients with demonstrated glucose hypometabolism as measured by FDG-PET will derive benefit from treatment.

The requestors have submitted to CMS various reasoned statements, including an unpublished document with their own decision model, which support coverage of FDG-PET primarily based upon evidence that this technology can identify patients with the anatomic lesions characteristic of AD more accurately than standard clinical evaluation. The decision analysis draft manuscript submitted compares two strategies for diagnosing patients with AD. In the first strategy, patients are diagnosed with AD using AAN guidelines. In the second strategy, patients with cognitive decline receive an FDG-PET scan to diagnose AD. In the latter strategy, the FDG-PET scan replaces certain steps of the recommended clinical evaluation required for the diagnosis of dementia or MCI (i.e., assessing whether cognitive decline affects multiple cognitive domains; presence of functional impairment; repeat visits in patients with MCI). The requestors conclude that this strategy, by identifying patterns of temporo-parietal hypometabolism in patients with cognitive decline, would better predict response to treatment beyond what can be predicted from clinical evaluation.

Although the second strategy has the potential to make the diagnosis of AD earlier (e.g., individuals with MCI who would not have to wait for a repeat visit), no data are available on whether the treatments are effective for patients chosen through the second strategy in the decision analysis. The pool of patients detected with FDG-PET would be different from those identified with a standard clinical evaluation that have been involved in studies of treatment efficacy. As mentioned above, the only demonstrated approach for predicting drug benefit for patients with AD is the standard clinical evaluation. This approach, for instance, may identify patients with factors other than glucose hypometabolism that are also affected by AChE-I agents. In fact, preliminary reports suggest that AChE-I may be effective in improving symptoms of persons with non-AD dementias (e.g., vascular dementia).[44] Thus, in the second strategy, treatments may not be effective for patients with positive FDG-PET scans who do not have dementia; alternatively, treatments may have a positive effect on patients with dementia and negative FDG-PET scans. Until other diagnostic procedures are shown to be more discriminating, the standard clinical evaluation remains the only predictor of treatment response for which there is evidence.

CMS considered a number of additional claims regarding use of FDG-PET contained in the request for coverage, discussed during MCAC deliberations, with experts and requestors, and also addressed in the expert opinion, position statements and decision model manuscript submitted during the course of the review process. A summary of these considerations follows.

Proponents indicated that treatment for AD should be started as early as possible and argued that diagnosis with FDG-PET would lead to earlier treatment. They cited studies showing that “delay of initiation of AChE-I therapy results in a smaller magnitude of benefit compared to patients who are treated earlier in their disease course”.[45] Although earlier drug treatment is likely to be beneficial, it is not clear how use of FDG-PET would prompt treatment at an earlier date than would a standard clinical evaluation. As discussed in the decision model, patients presenting with cognitive decline and diagnosed by clinical evaluation with MCI or with mild to moderate dementia attributable to AD are candidates for drug therapy. The decision to treat is not contingent upon the results of an FDG-PET scan. Rather than ordering an additional test following the standard clinical evaluation, the preferred strategy is to recommend drug therapy without further delay.

It was also proposed that the information provided by FDG-PET would support better planning for care giving and end-of-life decisions. Although there is no empirical evidence to support this view, enhanced ability on the part of patient and caregivers to engage in financial, legal and medical planning would be an important outcome if shown to be the case. However, all elderly patients clinically diagnosed with MCI or with dementia need assistance with these types of decisions. They are likely to benefit from medical and educational interventions regarding progressive cognitive impairment during follow up visits. In order to support their view, test proponents would have to show the value of FDG-PET in this clinical context for distinguishing between AD and other neurodegenerative causes of dementia.

Proponents suggested that clinical assessments require multiple tests performed over several years to reach an accurate diagnosis of AD whereas a single FDG-PET can reach greater accuracy early in the disease, thus avoiding excessive visits, additional tests, and additional evaluations. However, the need for longitudinal follow-up visits after an initial assessment of declining cognitive function in elderly patients is not justified solely by the goal of achieving an increasingly accurate diagnosis of AD over time. The progressive nature of cognitive impairment and the increased presence of co-morbidities make continuity of care particularly relevant in patients with AD as well as other neurodegenerative diseases. In addition, patients and their families often need time and continuing support to adjust to the diagnosis of dementia.[46] Finally, suggestive but inconclusive FDG-PET imaging studies might also require additional FDG-PET testing in subsequent visits.

Another concern raised in a letter submitted by experts from UCLA was the under-recognition of dementia in primary care settings. The authors noted that “because of the lack of information about dementia and lack of use of standardized approaches, primary care practitioners under-diagnose AD and other dementias in clinical practice.” Although the authors suggested that the availability of FDG-PET would “greatly assist the community practitioner in the early diagnosis and treatment of patients with AD,” they provided no support for this assertion of the value of testing. Primary care physicians often initiate a clinical assessment when patients present with symptoms that raise the suspicion of dementia. If findings of the initial assessment are abnormal, referral for further neurological, psychiatric, or neuropsychological evaluation is a common next step.[47] A primary care clinician that fails to detect declining mental function during the initial clinical evaluation would also fail to order an FDG-PET scan. Moreover, although considered by CMS, this use of FDG -PET was not included in the coverage request.

UCLA experts also asserted an advantage of FDG-PET over the standard clinical evaluation related to nursing home utilization. In the submitted decision model draft manuscript, they calculated that several extra months of nursing home care would be needed for each patient with AD-related cognitive decline that failed to receive treatment after the standard clinical evaluation. As the TA report demonstrates, however, the preferred strategy is to treat all patients diagnosed by standard clinical evaluation with MCI or dementia of possible or probable AD etiology. Treatment would then be offered to all such patients (including those who would receive a positive FDG-PET scan if the test were performed). It is the treatment rather than the test that may delay nursing home placement.

Additional issues raised that were not explicitly addressed in the TA described above were (1) the effect of FDG-PET use upon patient adherence to drug treatment and (2) the positive and negative psychosocial labeling effects of FDG-PET tests on patients with AD and MCI. However, no empirical information or data was available pertaining to these issues that would alter the review and interpretation of the quantitative evidence presented in the TA.

Therefore, in spite of its apparently favorable operating characteristics in identifying AD-specific lesions, FDG-PET has not been shown to predict response to treatment beyond what can be predicted from the standard clinical evaluation as recommended by the AAN. Future studies using FDG-PET results as inclusion criteria in treatment trials may provide evidence of the utility of FDG-PET scans, at which time CMS would need to re-evaluate such evidence. Particularly useful would be studies addressing the difference in outcomes of individuals in whom the standard evaluation and the strategy with FDG-PET yield discordant diagnoses. In addition to cognitive and functional status, study outcomes could include treatment decisions, time to accurate diagnosis, rates of hospitalization, caregiver arrangements, and other outcomes deemed to be important in patients with symptoms of dementia.

In addition, requestors could potentially reformulate the TA decision model to address these outcomes of interest or modify model input parameters as new evidence becomes available to support those changes. Also, there may be specific clinical circumstances in which FDG-PET would be particularly useful. If so, CMS would consider narrowly defined uses of FDG-PET in patients with cognitive decline should requests for defined patient subgroups be submitted in the future. For instance, patients with fronto-temporal dementia who may be difficult to distinguish clinically from patients with AD may constitute such a case where functional neuroimaging could prove beneficial. For this purpose, CMS would consider methodologies other than randomized controlled trials comparing FDG-PET and a standard clinical evaluation. Studies could supplement research evidence with rigorously structured expert decision analyses of clinical scenarios involving various practice settings and affecting specific patient subgroups.

Decision

As described in this decision memorandum, we have analyzed the medical and scientific evidence submitted with the request for a national coverage decision, as well as additional information obtained as a result of our own investigation. The TA demonstrates that adding an FDG-PET scan to the standard work-up of AD does not improve upon the practice of routinely treating patients with the diagnosis of mild cognitive impairment or dementia of possible or probable AD type, as defined by AAN clinical guidelines. Our analysis concludes that the addition of an FDG-PET scan to the standard evaluation of AD does not result in improved patient outcomes.

Therefore, we have determined that the available evidence is adequate to conclude that an FDG-PET scan is not reasonable and necessary when used in the diagnosis and management of early dementia in elderly patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease.

Therefore, we intend to continue our national noncoverage decision. This noncoverage policy will apply to those patients that present with cognitive decline (i.e., suspected dementia) and are clinically diagnosed with age-related memory impairment, MCI, or mild, moderate or severe dementia. Patients along this clinical continuum of cognitive decline encompass those for whom AD is suspected as a contributing etiology and specifically includes patients diagnosed with possible or probable AD by AAN-recommended criteria and those diagnosed with other neurodegenerative diseases with or without AD.

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1 http://www.alzheimers.org/generalinfo.htm#howmany.

2 Petersen RC et al. Practice parameter: Early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. May 2001.

3 http://www.alzheimers.org

4 Ince P et al. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. The Lancet. January 2001.

5 Knopman DS et al. Practice parameter: Diagnosis of dementia (an evidence-based review), Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. May 2001.

6 Mohs RC et al. A 1-year placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology. August 2001.

7 AAN recommends that Diagnostic and Statistical Manual, 3rd edition (DSM-IIIR) clinical criteria for AD and the National Institute of Neurologic, Communicative Disorders and Stroke - AD and Related Disorders Association (NINCDS - ADRDA) criteria for the diagnosis of probable AD should be routinely used. NINCDS-ADRDA criteria for probable AD require:1) presence of dementia, 2) onset between 40 and 90 years of age, 3) impairment in two or more cognitive areas, 4) progression of deficits > 6 months, 5) undisturbed consciousness, and 6) absence of other reasonable diagnosis. Possible AD can be diagnosed in the presence of a single, gradually progressive area of cognitive deficit (e.g., memory loss).

8 Getsios D, et al. Assessment of health economics in Alzheimer's disease (AHEAD): galantamine treatment in Canada. Neurology. September 2001.

9 Rockwood K, et al. Effects of a flexible galantamine dose in Alzheimer's disease: a randomized, controlled trial. Journal of Neurology, Neurosurgery and Psychiatry. November 2001.

10 Burns A et al. The effects of donepezil in Alzheimer's disease: Results from a multinational trial. Dementia and Geriatric Cognitive Disorders. 1999.

11 Centers for Medicare & Medicaid Services. Coverage Issues Manual. Section 50-36. FDG Positron Emission Tomography http://www.cms.gov/manuals/06_cim/ci50.asp#sect_50_36. January, 2001.

12 Centers for Medicare & Medicaid Services. FDG Positron Emission Tomography Decision Memorandum. http://www.cms.hhs.gov/ncdr/memo.asp?id=85. December 2000.

13 Federal Register: March 10, 2000 (Volume 65, Number 48) Notices. Pages 12999-13010.

14 67 Federal Register 66757

15 67 FR 66757

16 Since neuroanatomic imaging testing was already incorporated within the scope of the AAN standard clinical evaluation, the EPC did not address any neuroimaging modalities other than FDG-PET.

17 Use of FDG-PET for asymptomatic patients with family history of AD meets the current definition of a screening service under the Medicare program and is therefore not a reimbursable benefit. See 42 C.F.R. § 411.15 (a) regarding particular services excluded from coverage, including “examinations performed for a purpose other than treatment or diagnosis of a specific illness, symptoms, complaint, or injury (…).”

18 Matchar DB, Kulsingham SL, McCrory DC, et al. Technology Assessment: Use of Positron Emission Tomography and other Neuroimaging Techniques in the Diagnosis and Management of Alzheimer’s Disease and Dementia. Duke Evidence-based Practice Center. December 2001. Available on the CMS website at http://www.cms.hhs.gov/ncdr/tadetails.asp?id=64.

19 See Technology Assessment report for additional inclusion criteria, article quality scoring, search strategy and other methodological aspects of the systematic review of the literature and model construction.

20 As previously noted, the population of asymptomatic individuals with a family history of AD was not part of the CMS analysis to arrive at a coverage determination.

21 The names and affiliation of expert consultants and peer-reviewers are listed in the TA report. Pages 112-113.

22 Matchar DB et al. Technology Assessment. Duke EPC. December 2001. Pages 86 and 87.

23 Silverman DH et al. Running title*:* Clinical Benefit of Incorporating FDG-PET into the Evaluation of Early Dementia. March 2002. This manuscript was presented as a reformulated analysis of an article previously published by D Silverman et al. Evaluating early dementia with and without assessment of regional cerebral metabolism by PET, A comparison of predicted costs and benefits. Journal of Nuclear Medicine. February 2002.

24 Under the charter then in effect, the MCAC EC could perform a variety of functions including “consider[ing] and act[ing] upon requests for assessments and tasks as may be requested by [CMS] during the year”. (MCAC charter as referenced in 63 FR 68780).

25 It should be noted that basic definitional issues in this area of clinical practice are not entirely resolved. The following are recommendations recently issued by the AAN in its most recent practice parameter on dementia regarding the need for clarification of dementia-related terms:

- (…)"The definition of the specific, common diseases that cause dementia – Alzheimer's disease, vascular dementia, dementia with Lewy bodies (DLB) and frontotemporal dementia – should be refined to minimize incompatibilities and confusing overlap between categories.
- The diagnosis of MCI also should be integrated with the definition of dementia as well as the definitions of specific diseases. As we move into an era of earlier recognition of cognitive impairment, clarification of the distinctions between no cognitive impairment, MCI, and early dementia is needed."

26 Knopman DS et al. Practice parameter: Diagnosis of dementia (an evidence-based review), Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. May 2001.

27 Doody RS et al. Practice parameter: Management of dementia (an evidence-based review), Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. May 2001.

28 Petersen et al. Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review), Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. May 2001.

29 Knopman DS et al. Practice parameter: Diagnosis of dementia (an evidence-based review), Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. May 2001.

30 American College of Radiology. March 2002.

31 National Electrical Manufacturers Association, March 2002.

32 Alzheimer’s Association. April 2002.

33 Society of Nuclear Medicine. January 2002.

34 Markin RE. Alzheimer’s Research Foundation. February 2002

35 UCLA. Alzheimer’s Disease Center. February 2002.

36 Only results from the Technology Assessment pertaining to elderly patients with mild to moderate dementia or with MCI are discussed in this section. Scenario C, asymptomatic patients with family history of AD, is not addressed since screening for AD in asymptomatic persons is not a Medicare benefit. See 42 C.F.R. § 411.15 (a)(1). Furthermore, this indication was neither included in the request for coverage nor considered or voted upon by the MCAC DI panel.

37 Burns A et al. The effects of donepezil in Alzheimer's disease: Results from a multinational trial. Dementia and Geriatric Cognitive Disorders. 1999.

38 False negatives = Patients with clinical and pathological characteristics of AD who receive a negative PET.

39 Technology Assessment. Tables 9a and 9b. Page 65.

40 True negatives = Patients with clinical characteristics of AD but without the pathological changes of AD who have a negative PET.

41 Technology Assessment. Table 9A Page 65.

42 Technology Assessment. Table 1: Model assumptions. Page 36.

43 It has not yet been established that severity of cerebral AD-specific pathology per se is associated with dementia. See Ince P et al. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. The Lancet. January 2001. Given the lack of direct correlation between AD-specific neuropathological findings and degree of cognitive failure, it is not even clear that availability of brain biopsy would lead to better drug therapy decisions.

44 Poole R. Donepezil effective in vascular dementia. Inpharma Weekly. 1326:11-12. February 23, 2002.

45 UCLA. Alzheimer's Disease Center. February 2002.

46 Agency for Health Care Policy and Research. Clinical Practice Guideline Number 19: Recognition and Initial Assessment of Alzheimer's Disease and Related Dementias. November 1996.

47 *Ibid*.

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